

REMARKS

This amendment is responsive to the final Office Action mailed May 14, 2008. Claims 61, 65-70, 72-76, and 84-99 were pending and under consideration. No claims are amended, cancelled, or newly presented for consideration in the present paper. Thus, claims 61, 65-70, 72-76, and 84-99 remain pending and under consideration.

I. The Provisional Double-Patenting Rejection

Claims 61, 65-70, 72-76 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 23, 38, 39, 45-62, and 64 of copending US Application No. 10/418,780 ("the '780 application"). Applicants note that the '780 application has been allowed and respectfully submit that the claims of the instant application are not obvious variants of the claims allowed in connection with the '780 application. Applicants therefore respectfully request reconsideration and withdrawal of the provisional double patenting rejection of claims 61, 65-70, 72-76.

II. The Rejection of Claims 61, 65-70, 72-76, and 84-99 as Obvious Should Be Withdrawn

Claims 61, 65-70, 72-76, and 84-99 are again rejected under 35 U.S.C. § 103(a) as allegedly obvious over Shachter, 2001, *Curr. Opin. Lipidol.* 12:297-304 ("Shachter") in view of GenBank Accession No. NT_035088, Jong *et al.*, 1999, *Atheroscler. Thromb. Vasc. Biol.* 19:472-484 ("Jong"), Senior, 2002, *Drug Discov. Today* 7:840-1 ("Senior") and Monia *et al.*, U.S. Patent No. 6,300,132 ("Monia").

The PTO Does Not Provide a Prima Facie Case of Obviousness

In brief, the PTO contends that Shachter teaches that variation in apolipoprotein C-III expression affects hypertriglyceridemia and that apolipoprotein C-III has an important role in elevating plasma triglyceride concentrations. The PTO contends that Senior teaches antisense inhibitors, albeit inhibitors of apolipoprotein B, as effective treatment approaches for hypercholesterolemia, and that antisense compounds can be delivered *in vivo* in a mouse model of hypercholesterolemia to decrease plasma triglyceride concentrations. The PTO contends that Jong teaches that apolipoprotein Cs have distinct effects on the major metabolic pathways and implies that changes in human apolipoprotein C expression may play a role in the etiology of human hyperlipidemias. The PTO cites Monia as teaching administration of antisense oligonucleotides, including chemically modified oligonucleotides, and contends that Monia provides a detailed blueprint for how to make and use inhibitory antisense oligonucleotides to target any known gene. The PTO also notes that GenBank Accession No.

NT_035088 teaches a nucleic acid sequence encoding apolipoprotein C-III as recited by SEQ ID NO:4.

In response, Applicants argued that none of the cited references, either alone or in combination, suggests to the artisan of ordinary skill that antisense compounds 100% complementary to SEQ ID NO:4 could or should be used in methods for ameliorating hepatic steatosis or lowering liver tissue triglyceride levels in an animal and fail to provide a reasonable expectation that such methods would succeed. More specifically, Applicants explained that none of the cited references, whether considered alone or in combination, teach or suggest that antisense inhibition of apolipoprotein C-III might result in amelioration of hepatic steatosis or reduction in *liver* triglyceride levels in an animal. Thus, Applicants argued that the presently claimed methods for ameliorating hepatic steatosis or lowering liver tissue triglyceride levels are not obvious in view of the cited references whether considered alone or in combination.

In the Office Action dated May 14, 2008, the PTO considered but rejected Applicants' arguments. In particular, the PTO indicated that the cited references, particularly Jong and Shachter, were relied upon to provide a reason to modulate apolipoprotein C-III expression. For example, the PTO pointed out that both Jong and Shachter suggest that apolipoprotein C-III may play a role in hypertriglyceridemia. *See* Office Action, p. 4. According to the PTO, these teachings provide an artisan of ordinary skill a reason to design an oligonucleotide to vary or reduce ApoC-III expression. *See id.* In the remainder of the Office Action, the PTO goes on to explain that the cited combination of references provide both motivation and a reasonable explanation of success for using antisense compounds that reduce apolipoprotein C-III expression in reducing plasma triglyceride levels.

However, nowhere does the PTO identify where the cited combination of references teaches or suggests that such antisense compounds could be used to ameliorate hepatic steatosis, as recited by claim 61 and the claims depending therefrom. In fact, none of the references, whether considered alone or in combination, teach anything regarding any role for apolipoprotein C-III in hepatic steatosis, or even remotely suggest, let alone provide a reasonable expectation of success, that reduction of apolipoprotein C-III expression might result in amelioration thereof. Similarly, nothing in either Shachter or Jong indicates that reduction of apolipoprotein C-III expression might result in reduced *liver* triglyceride levels as recited by claims 70 and the claims depending therefrom. Indeed, as noted in Applicants' previous response, both Shachter and Jong equivocate rather than conclude that reduction of apolipoprotein C-III expression causes reduced *plasma* triglyceride levels. *See, e.g.,* Shachter, paragraph bridging pp. 298-9 and Jong, paragraph bridging pp. 473-4. While the

PTO may disagree with this characterization of the references' teachings relating to such plasma triglyceride levels, the PTO must still provide a reason, apparent from the cited references, to modify the references to obtain Applicants' methods for ameliorating hepatic steatosis or lowering *liver* triglyceride levels. *See KSR. Int'l Co. v. Teleflex*, 127 S.Ct. 1727, 1731 (2007) and *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007).

However, even assuming *arguendo* that Shachter and Jong show that reduced apolipoprotein C-III expression causes reduced *plasma* triglyceride levels, the PTO still has not provided a reason, apparent from the cited references, to modify the references to obtain Applicants' methods for ameliorating hepatic steatosis or lowering *liver* triglyceride levels. Nowhere in the references cited by the PTO, whether considered alone or in combination, is there any suggestion that hepatic triglyceride levels should necessarily follow plasma triglyceride levels. Thus, even assuming *arguendo* that the cited references suggest that reduction of apolipoprotein C-III expression might reduce plasma triglyceride levels, the combination of references fails to suggest that reduction of apolipoprotein C-III expression might ameliorate hepatic steatosis or lower liver triglyceride levels.

Accordingly, for the reasons discussed above, the invention as presently claimed is not *prima facie* obvious over the references cited by the PTO, whether considered alone or in combination..

The Cited Art Teaches Away from the Claimed Invention

In addition, the cited combination of references actually teaches away from the invention as presently claimed. As one of ordinary skill in the art at the time the present application was first filed would be well aware, apolipoprotein C-III plays a complex role on triglyceride metabolism, with both stimulatory and inhibitory effects on different components of the system. For example, Jong reports that apolipoprotein C-III inhibits lipolysis of triglyceride-containing lipoprotein and uptake of VLDL components by the liver, but stimulates cholesteryl ester transfer protein. *See Jong* at p. 475, col. 2, first and second full paragraph ("apoC3 completely abolished the apoB-mediated binding of lipoproteins to the LDLR [low density lipoprotein receptor expressed by hepatocytes]") and at Table 3.

Similarly, Shachter indicates that apolipoprotein C-III has been shown "to directly interfere with their [triglyceride-rich emulsions and lipoprotein] hepatic clearance." *See Shachter*, p. 297, Col. 2, second paragraph. Thus, one of the functions of expressed apolipoprotein C-III protein is to *reduce* uptake of triglycerides by the liver. Accordingly, one skilled in the art might expect from these teachings that reduction of apolipoprotein C-III

would lead to increased hepatic uptake of triglycerides and ultimately lead to increased triglyceride accumulation in the liver and hepatic steatosis since Jong and Shachter both suggest that expressed apolipoprotein C-III inhibits binding of lipoproteins to the LDLR receptor and hepatic clearance of lipoprotein particles.

Unexpectedly, Applicants found the opposite to be true, *i.e.*, that reduction of apolipoprotein C-III expression resulted in amelioration of hepatic steatosis and lowering of *liver* triglyceride levels. Thus, Jong and Shachter actually *teach away* from the invention as presently claimed, further demonstrating the non-obviousness of the claimed methods. *See In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). In view of this teaching away, and lacking any suggestion from the cited references that reduction in apolipoprotein C-III expression might achieve the claimed effects, the instant claims cannot be obvious over this combination of references. *See Aventis Pharma Deutschland GmbH v. King Pharms, Inc.* 499 F.3d 1293, 1301 (Fed. Cir. 2007).

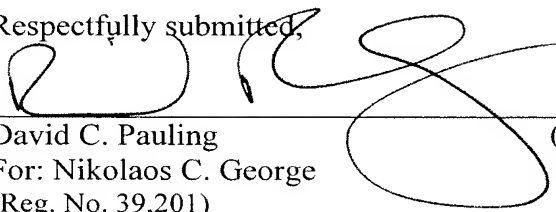
Applicants respectfully submit that the PTO has failed to articulate a reason why the artisan of ordinary skill should modify the cited references, either alone or in combination, to achieve the invention as presently claimed. Further, Applicants respectfully submit that such an ordinarily-skilled artisan could not predict the effectiveness of the claimed methods in view of the general guidance provided by the cited references. Finally, Applicants respectfully submit that the cited references actually teach away from the presently claimed methods. As such, Applicants respectfully submit that claims 61 and 70, and each of the claims depending therefrom, are not obvious over the references cited by the PTO. Therefore, Applicants respectfully request that the rejection of claims 61 and 70 under 35 U.S.C. § 103(a) as allegedly obvious over Shachter in view of Jong, Senior, Monia, and GenBank Accession No. NT_035088 be withdrawn.

III. Conclusion

In light of the above remarks, the Applicant respectfully requests that the PTO reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (650) 739-3949, if a telephone call could help resolve any remaining items.

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Respectfully submitted,


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